FPN: 68P

# Phase 2 Results of Ivonescimab, a Novel PD-1/VEGF Bispecific in Combination with Chemotherapy for First Line treatment of Patients with Advanced/Metastatic Squamous Non-small Cell Lung Cancer (NSCLC)


Li Zhang[1], Wenfeng Fang[1], Yuanyuan Zhao[1], Yunpeng Yang[1], Ningning Zhou[1], Likun Chen[1], Yan Huang[1], Jianhua Chen[2], Li Zhuang[3], Yingying Du[4], Qitao Yu[5], Wu Zhuang[6], Yanqiu Zhao[7], Ming Zhou[8], Weidong Zhang[9], Yu Zhang[10], Yixin Wan[11], Michelle Xia[12]

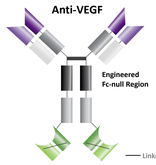
1. Sun Yat-Sen University Cancer Center, Guangzhou, P. R. China; 2. Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China; 3. The First Affiliated Hospital of Anhui University, Hefei, P. R. China; 4. Hunan Cancer Hospital, Changsha, P. R. China; 5. Hunan Cancer Hospital/The Affiliated Cancer, Hospital of Xiangya School of Medicine, Central South University, Changsha, China; 6. Cancer Hospital of Sichuan Province, Chengdu, China; 7. Guangxi Medical University Cancer Hospital, Nanning, P. R. China; 8. Zhejiang Cancer Hospital, Hangzhou, China; 9. Summit Therapeutics, Inc.; Menlo Park, CA, USA; 10. The Radiology Experts, Inc.; 11. Akeso Biopharma, Inc., Zhongshan, P. R. China


## BACKGROUND

Since the initial approval of bevacizumab (bev) with chemotherapy (chemo) in non-small cell lung cancer (NSCLC), the subsequent study of bev in combination with PD-1 therapy for first line metastatic disease has been focused on patients with non-squamous (non-Sq) NSCLC histology. Ivonescimab is a novel anti-PD-1/VEGF bispecific antibody. The bispecific approach to these targets has the potential to recalibrate the malignant immuno-architecture in favor of a more immune responsive anti-tumor microenvironment. In this trial, we aimed to assess the efficacy and safety of ivonescimab combined with chemotherapy for first line advanced or metastatic NSCLC in patients (pts) with squamous (Sq) or non-Sq NSCLC.[1]

### Ivonescimab (AK112/SMT112): First in Class* PD-1/VEGF

**Brings two validated oncologic mechanisms into ONE novel tetravalent molecule[2,3,4]**




**Designed to potentially improve the balance of anti-tumor activity and safety**

### Ivonescimab Mechanism Of Action

**Cooperative Binding**

Potential to drive synergistic anti-tumor activity[2,5,8]

**Increased Avidity in Tumor Microenvironment (TME)**
VEGF binding increases affinity to PD-1 by >18X[6]
PD-1 binding increases affinity to VEGF by >4X[6]
*(in vitro)*

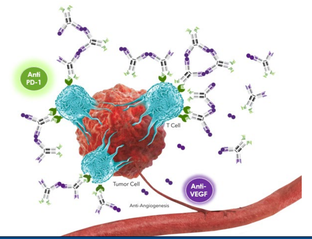
**Enhanced Activity of T Cells**
VEGF dimer leads to potential interconnection of ivonescimab molecules, which may increase activity of T cells[6,7]
*(in vitro)*

**Potential to accumulate higher levels of ivonescimab in the TME vs. healthy tissue**
- Higher levels of PD-1 & VEGF expression in TME[1,7,9]

**T1/2 of 6-7 days[10] provides blockade of both targets and with its affiliated clearance, could potentially lead to a favorable safety profile[8,9]**

**Engineered Fc-null region could lead to reduced adverse events**
- Humanized IgG1 bispecific antibody[8]
- Via reduction of ADCC, ADCP, and CDC in-vitro[5,11] and no meaningful infusional cytokine release (IL-6 and TNF-α) in patients[5]

***There are no known PD-1-based bispecific antibodies approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).**

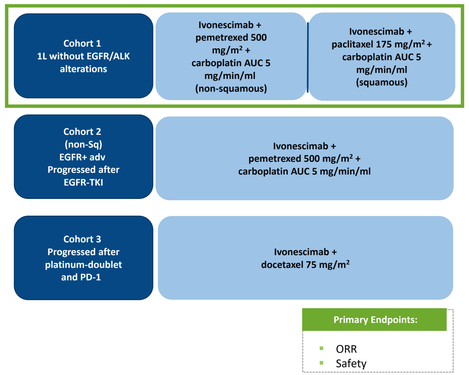



## METHODS

An open-label, multi-center phase II study evaluating the efficacy and safety of ivonescimab combined with chemotherapy in pts with advanced or metastatic NSCLC. Pts were enrolled into 3 cohorts based on prior therapy and presence of actionable genomic alterations (AGA). In pts with NSCLC without AGA receiving first line therapy for advanced/metastatic disease, pts were treated with 10 or 20 mg/kg ivonescimab once every 3wks combined with carboplatin and pemetrexed (non-Sq) or carboplatin and paclitaxel (Sq). The primary endpoint was ORR per RECIST 1.1 by investigator. (Figure 1, Cohort 1).
Data from pts with advanced or metastatic disease were presented in ASCO 2023 including data for first line Sq and non-Sq pts. In this poster we report additional pts and longer follow-up data from all the cohorts from the study (Table 4, results from Cohorts 2 and 3).

### Figure 1. Study Design[1]

NCT04736823




### Baseline Characteristics

As of data cut-off Oct 10, 2023, 135 pts with advanced or metastatic NSCLC were enrolled and received ivonescimab plus chemotherapy, including 63 with Sq and 72 pt with non-Sq. Median age was 61 yrs. 77.8% male, 3% and 97% pts had ECOG PS 0 and 1, respectively, the majority (86%) had stage IV disease, and 20% pts had brain metastasis at baseline.
See Table 1 for Baseline Characteristics.

### Table 1. Baseline Characteristics

| | Squamous NSCLC (N = 63) | Non-Squamous NSCLC (N = 72) | Total (N = 135) |
|---|---|---|---|
| Age (yr) - Median (Range) | 59.0 (40, 75) | 61.0 (37, 72) | 61.0 (37, 75) |
| Male, n(%) | 52 (82.5) | 53 (73.6) | 105 (77.8) |
| ECOG PS 1, n(%) | 61 (96.8) | 70 (97.2) | 131 (97.0) |
| Smoking Status, n(%): | | | |
| Former or Current | 47 (74.6) | 43 (59.7) | 90 (66.7) |
| Never | 16 (25.4) | 29 (40.3) | 45 (33.3) |
| PD-L1 TPS, n(%): <1% | 24 (38.1) | 38 (52.8) | 62 (45.9) |
| 1-49% | 24 (38.1) | 17 (23.6) | 41 (30.4) |
| ≥50% | 14 (22.2) | 15 (20.8) | 29 (21.5) |
| Stage IV, n(%) | 45 (71.4) | 71 (98.6) | 116 (85.9) |
| Distant metastatic sites >=3, n(%) | 13 (20.6) | 36 (50.0) | 49 (36.3) |
| Brain metastasis, n(%) | 5 (7.9) | 22 (30.6) | 27 (20.0) |
| Liver metastasis, n(%) | 10 (15.9) | 14 (19.4) | 24 (17.8) |
| Bone metastasis, n(%) | 13 (20.6) | 35 (48.6) | 48 (35.6) |
| Central tumor, encasement, n(%) | 38 (60.3) | N/A | N/A |
| Tumors with Necrosis/Cavitation, n(%) | 12 (19.0) | N/A | N/A |
| Invasion of Large Vessels, n(%) | 9 (14.3) | N/A | N/A |
| History of Hemoptysis, n(%) | 13 (20.6) | N/A | N/A |

## SAFETY

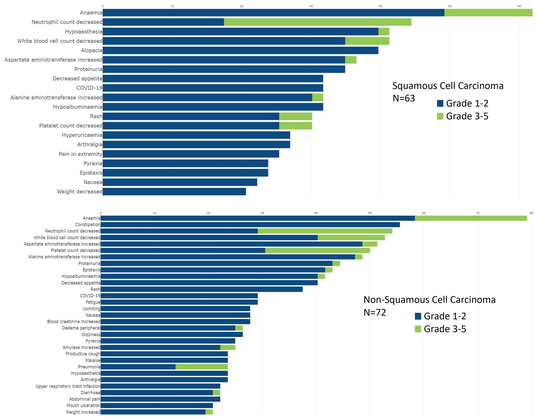
### Table 2. Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC Safety Results

| Summary of Safety | Non-Squamous (N = 72) n (%) | Squamous (N = 63) n (%) |
|---|---|---|
| Grade ≥3 TEAE | 41 (56.9%) | 42 (66.7%) |
| Grade ≥3 TRAE | 18 (25.0%) | 28 (44.4%) |
| TESAE | 28 (38.9%) | 27 (42.9%) |
| TRSAE | 14 (19.4%) | 18 (28.6%) |
| TEAE Leading to ivonescimab discontinuation | 2 (2.8%) | 7 (11.1%) |
| TRAE Leading to ivonescimab discontinuation | 2 (2.8%) | 7 (11.1%) |
| TEAE Leading to Death | 8 (11.1%) | 4 (6.3%) |
| TRAE Leading to Death | 3 (4.2%) | 0 |

TEAE: treatment-emergent adverse event.
TRAE: treatment-related adverse event.
TESAE: treatment-emergent serious adverse event.
TRSAE: treatment-related serious adverse event.

The most common treatment-emergent adverse events (TEAEs) in pts with Sq histology were anemia, neutrophil count decreased, and hypoesthesia. In pts with non-Sq histology, they were anemia, constipation, and neutrophil count decreased (details see figures above). Grade ≥3 TEAEs occurred in 66.7% and 56.9% of pts in Sq and non-Sq, respectively.

### Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC TEAE ≥20% (%)




### Table 3. Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC Adverse events of interest

**Immune-related Adverse Events**

| Adverse Event in >1% | Total (N = 135) Any Grade (%) | Total (N = 135) Grade 3+ (%) |
|---|---|---|
| Amylase increased | 4 (3.0) | 0 |
| Hypothyroidism | 6 (4.4) | 0 |
| Immune-mediated lung disease | 7 (5.2) | 3 (2.2) |
| Rash | 5 (3.7) | 2 (1.5) |
| Diarrhoea | 5 (3.7) | 2 (1.5) |
| Aspartate aminotransferase increased | 2 (1.5) | 0 |
| Lipase increased | 4 (3.0) | 2 (1.5) |
| Platelet count decreased | 4 (3.0) | 3 (2.2) |
| Hyperthyroidism | 3 (2.2) | 0 |

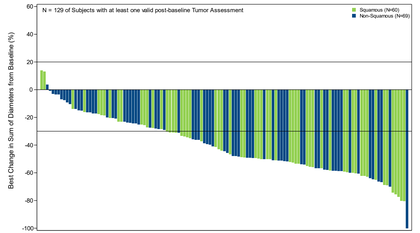
**Potential VEGF-related Adverse Events**

| Adverse Event in >1% | Non-Sq (N=72) | | Sq (N=63) | |
|---|---|---|---|---|
| | Any Grade (%) | Grade ≥3 (%) | Any Grade (%) | Grade ≥3 (%) |
| Proteinuria | 33 (45.8) | 1 (1.4) | 22 (34.9) | 0 |
| Epistaxis | 31 (43.1) | 1 (1.4) | 15 (23.8) | 0 |
| Blood pressure increased | 8 (11.1) | 1 (1.4) | 12 (19.0) | 1 (1.6) |
| Hypertension | 7 (9.7) | 3 (4.2) | 10 (15.9) | 4 (6.3) |
| Hemoptysis | 7 (9.7) | 0 | 9 (14.3) | 1 (1.6) |
| Gingival bleeding | 8 (11.1) | 0 | 8 (12.7) | 0 |
| Hematochezia | 3 (4.2) | 0 | 4 (6.3) | 0 |
| Hematuria | 0 | 0 | 4 (6.3) | 0 |
| Vaginal hemorrhage | 2 (2.8) | 0 | 0 | 0 |
| Embolism venous | 1 (1.4) | 0 | 1 (1.6) | 0 |

## RESULTS

### Ivonescimab Chemo Combination in 1L Advanced/Metastatic NSCLC
**Median follow up 21.3 months**

Percent Changes from Baseline in Target Lesions
Sum of Diameters (N=129*)

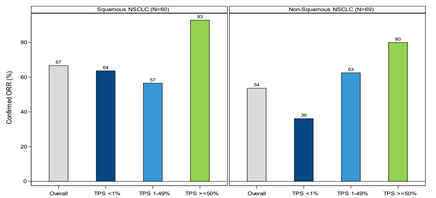



†ORR 62.2% (N=135)
*includes subjects with at least one post-baseline tumor assessment based on investigator assessment

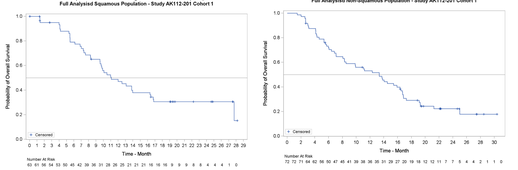
**ORR, DCR, and Median DOR**

| | Non-Squamous N = 72* | Squamous N = 63* |
|---|---|---|
| ORR† N (%) [95% CI] | 39 (54.2) (42.0, 66.0) | 45 (71.4) (58.7, 82.1) |
| DCR† N (%) [95% CI] | 69 (95.8) (88.3, 99.1) | 57 (90.5) (80.4, 96.4) |
| Median DOR, mo [95% CI], mo | 15.4 [11.1, 17.9] | 12.7 [8.1, NE] |

*includes subjects with at least one post-baseline tumor assessment, † ORR & DCR based on confirmed BOR, NE=Non-estimable

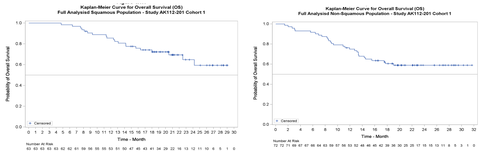



### Ivonescimab Chemo Combination 1L Advanced/Metastatic NSCLC
**Progression Free Survival (N=135)** Median follow up 21.3 months




| | Med PFS, mo (95% CI) | Est 9 mo PFS (95% CI) |
|---|---|---|
| Squamous NSCLC (N=63) | 11.1 (9.5, 16.3) | 65.1 (51.2, 75.9) |
| Non-Squamous NSCLC (N=72) | 13.3 (8.3, 16.4) | 58.9 (46.5, 69.4) |

### Ivonescimab Chemo Combination 1L Advanced/Metastatic NSCLC
**Overall Survival (N=135) - Median follow-up 22.1 months**




| | Med OS, mo (95% CI) | Est 9 mo OS (95% CI) |
|---|---|---|
| Squamous NSCLC (N=63) | NE (22.5, NE) | 90.4 (80.0, 95.6) |
| Non-Squamous NSCLC (N=72) | NE (17.5, NE) | 81.9 (70.9, 89.1) |

Median follow-up was 22.1 mo. Pts with Sq experienced a 71.4% ORR with median DOR 12.7 mo, 90.5% DCR, the 9-mo PFS and OS rate was 65.1% and 90.4%, respectively. Pts with non-Sq experienced a 54.2% ORR, median DOR 15.4 mo, 95.8% DCR, the 9-mo PFS rate and OS rate was 58.9% and 81.9%, respectively.

### Table 4. Updated Ivonescimab in Combination with Chemo in 2L for Cohorts 2 & 3

| | Cohort 2 (EGFR-TKI Relapsed NSCLC) N=19 | Cohort 3* (PD-1/Platinum Relapsed NSCLC) N=20 |
|---|---|---|
| Median Follow Up (range) | 25.8 (22.3 – 28.8) | 24.7 (22.1 – 26.3) |
| Confirmed ORR, % | 68.4 (43.4, 87.4) | 40.0 (19.1, 63.9) |
| DCR, % (95% CI) | 94.7 (74.0, 99.9) | 80.0 (56.3, 94.3) |
| DoR, mo (95% CI) | 8.7 (4.1, 16.6) | 12.7 (3.8, NE) |
| Median PFS, mo (95% CI) | 8.5 (4.1, 12.9) | 7.1 (2.2, 14.6) |
| Median OS, mo (95% CI) | 22.5 (10.4, NE) | 17.1 (8.4, NE) |
| Est 12 mo OS, % (95% CI) | 73.7 (47.9, 88.1) | 65.0 (40.3, 81.5) |
| Median duration of treatment (range), mo | 8.5 (1, 29) | 5.9 (1, 29) |
| Percentage of patients on treatment at 12 months | 6 (31.6) | 7 (35.0) |

*Cohort 3 n=7 (35%) are squamous and n=13 (65%) are non-squamous pts
In Sq, 5 (71%) and 2 (29%) pts received 1 and 2 prior line of therapy, respectively,
In non-Sq, 9 (69%), 3 (23%) and 1 (8%) pts received, 1, 2, and 3 prior line of therapy, respectively.

## CONCLUSION

- Ivonescimab plus chemotherapy has shown promising anti-tumor activity and safety profile in patients with advanced/metastatic NSCLC in this Phase 2 study.
- Ivonescimab was administered safely in combination with platinum doublet chemotherapy to patients with Squamous and Non-Squamous histology.
- Ivonescimab is currently being evaluated in 4 Phase III studies in NSCLC (HARMONi - NCT05184712; HARMONi-2 - NCT05499390; HARMONi-3 - NCT05899608; HARMONi-5 - NCT05840016)


### ACKNOWLEDGEMENTS

- We are grateful to the patients and their care givers, to investigators and all site staff who participated in the ivonescimab-201 study.
- This study was sponsored by Akeso Biopharma, Inc.
- Editorial assistance was provided by Summit Therapeutics, Inc.
- Please contact the author at zhangli@sysucc.org.cn for questions or comments
- The presenter declares no conflicts of interest to disclose.


### REFERENCES


1. Zhao Y., et al. JCO (June 01, 2022) 40, no. 16_suppl 9019; 2. Manegold C, et al. J Thorac Oncol 2017;12(2):194-207; 3. Pardoll, D. Nat Rev Cancer 2012;12(4):252-64; 4. Tamura R, et al. Med Oncol 2020;37(1):2; 5. Data on File. [14, 15] Summit Therapeutics Inc.; 6. Zhong T, et al. AACR-NCI-EORTC International Conference 2023.Poster #B123, Abstract #35333, Boston, MA, USA; 7. Zhong T, et al. JITC 2022;10(2):521.; 8. Zhao Y. et al., eClinicalMedicine. 2023; 3(62): 102106..; 9. Zhou C. et al., Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 9040.; 10. Zhang et al., ASCO 2023 poster #9087; 11. Huang et al Frontiers in immunology vol. 13 924542. 27 Jun 2022.